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THE PLANT DISEASE REPORTER

Issued by

THE PLANT DISEASE SURVEY, DIVISION OF MYCOLOGY AND DISEASE SURVEY
BUREAU OF PLANT INDUSTRY, SOILS, AND AGRICULTURAL ENGINEERING
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SUPPLEMENT 157

SYMPOSIUM ON NEW DEVELOPMENTS IN FUNGICIDES

Held at Cincinnati, December 9, 1944, in Connection with the Meeting of The American Phytopathological Society

April 15, 1945

The Plant Disease Reporter is issued as a service to plant pathologists throughout the United States. It contains reports, summaries, observations, and comments submitted voluntarily by qualified observers. These reports often are in the form of suggestions,queries,and opinions,frequently purely tentative,offered for consideration or discussion rather than as matters of established fact. In accepting and publishing this material the Division of Mycology and Disease Survey serves merely as an informational clearing house. It does not assume responsibility for the subject matter.

FOREWORD

In publishing the minutes of a symposium on new developments in fungicides the Reporter is departing somewhat from its recognized field of plant disease incidence and distribution. Search for new fungicides is a project of so much current importance that the report has been accepted for publication as an emergency service with no intention of implying a permanent expansion of the established scope of the Reporter and its Supplements.

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Notes by Howard P. Barss

Plant Disease Reporter
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The meeting started at about 8:30 P.M., under the chairmanship of Dr. H. C. Young of the Ohio Agricultural Experiment Station. He called attention to the radical changes going forward in the fungicide field. It was realized that the older fungicides are not satisfactorily meeting all needs. They are often not compatible with other materials which should be added for economical pest control, but in other cases they are not specific enough for particular purposes. It was suggested that in perhaps three to five years a more efficient and effective list of fungicides would be in evidence than ever seen before. Revolutionary changes of benefit to agriculture were held to be in sight. Reference was made to the prospect of using fungicides and insecticides in concentrated form with increased advantages and lower costs from the plant protection standpoint.

Discussions were opened on the four major topics selected for consideration, as follows:

1. Quaternary ammonium derivatives.--Discussion leader, Frank L. Howard
2. Carbamic acid group.--Discussion leader, J. W. Heuberger
3. Properties of the quinones.--Discussion leader, George L. McNew
4. Synergism and antagonism.--Discussion leader, James G. Horsfall

Unfortunately, the paper presented by Dr McNew cannot be included here. The other papers and discussions follow.

QUATERNARY AMMONIUM DERIVATIVES

By Frank L. Howard, Rhode Island Agricultural Experiment Station

In opening a discussion on new developments in fungicides, it seems well to consider briefly the basic reasons for the present forward surge in pesticide research. An urgent reason that might be given is the war-induced metal scarcity and the shortage of natural materials. Coupled with this, we have the interest of military authorities in the prevention of mold deterioration and in insect control. Another intangible current reason is the tacit government approval of such research by permitting the deduction of reasonable costs from corporate taxes. There has also been a fuller realization by the chemical industry of the potential magnitude of the pesticide field. Plant pathologists and entomologists have worked painstakingly during the past twenty years to make available screening tests for selecting fungicides and insecticides with fair reliability. Finally, perhaps, the greatest factor of all has been the spirit of teamwork that is making itself felt in which cooperation has replaced suspicion between investigators in industry and in tax-supported agencies. Today there is greater collaboration between chemists, horticulturists, entomologists, and pathologists in the development of pest control measures than ever before.

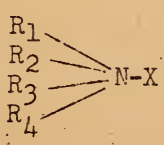
The development of soluble quaternary ammonium derivatives as fungicides has greatly aided the establishment of the concept of molecular or ionic dispersion of the toxicant for plant disease control. Heretofore, most fungicidal chemicals have been applied to plant surfaces in the particulate state rather than in solution, in spite of certain debatable advantages for the latter condition. Research has shown that the fungitoxicity of a given quantity of chemical varies directly with its surface area. Thus, greater efficiency might be expected from materials having the maximum area exposed as when dispersed as molecules or ions. In certain cases, fungicidal chemicals are more stable in solution than when desiccated to dry powders. Oftentimes, a solution of the product results from the manufacturing process which subsequently must be dried to provide a dust-like solid with the consequent added expense. More important is the fact that usually particulate fungicides only protect a plant surface or infection court from invasion by the pathogen, but specific soluble organic toxicants may both protect against infection and also serve as so-called "eradicant" or curative agents. The advantages of a combined protectant and therapeutant are obvious. Probably the most important future development in plant protection will be the development of selective synthetic organic chemicals for use in internal chemotherapy.

About three or four years ago, while examining the structural formulae of organic compounds that had proved to have high fungicidal potency in laboratory tests, it became apparent that a certain category of nitrogen-containing compounds were strong fungus inhibitors. From this the hypothesis of the effectiveness of certain linkages of "5-valent" nitrogen for the destruction of micro-organisms arose. Chemists tell us that elemental nitrogen has inherently 8 valences capable of use, but we find that in general either 3 or 5 are used. Dosage-response tests of the inhibition of fungous spore germination repeatedly have shown that compounds containing nitrogen in which only 3 valences were attached to

radicals or ions were usually of low or no fungicidal potency. However, when the configuration of the molecule is such that the nitrogen forming its nucleus or comprising a part of the nucleus exerts 5 of its valence bonds, we may expect a fungus-inhibiting material. To this class of compound, the term quaternary ammonium derivative has been applied. I believe that the basic structure can be best visualized by employing ammonium hydroxide, expressed empirically as NH_4 OH. The structure of the molecule is pictured as 4 hydrogen atoms each attached by a single bond to the nitrogen atom. This in turn is attached to a hydroxyl ion which has one bond from the oxygen attached to the nitrogen and the other bond attached to a hydrogen. When ammonium hydroxide is placed in water it has been found to dissociate into a NH_4 cation, a positive ion, and an OH anion, a negative ion. Chemists have found that the 4 hydrogen atoms of the cation are readily replaceable and that the hydroxyl anion can be replaced by an acid radical. An example of this replacement would be to add trimethyl amine $(CH_3)_3N$ to water and obtain trimethyl ammonium hydroxide $(CH_3)_3NHOH$. In this case 3 methyl radicals have replaced 3 hydrogen atoms and thus an organic quaternary ammonium compound is obtained, which upon dissociation gives the positive ion, $(CH_3)_3$ NH and the negative ion, OH.

At the present time four generic groups of the quaternary ammonium class of compounds have developed. These are substituted quaternary ammonium salts, typified by Zephirin (a complex of benzyl lauryl dimethyl ammonium chloride); phenyl mercuri triethanol ammonium salts, typified by Puratized N5D (phenyl mercuri triethanol ammonium lactate); 6-membered heterocyclic nitrogen ring compounds, typified by Isothan Q15 (lauryl isoquinolinium bromide); and combined 6- and 5-membered heterocyclic nitrogen ring compounds, typified by cationic nicotinium salts.

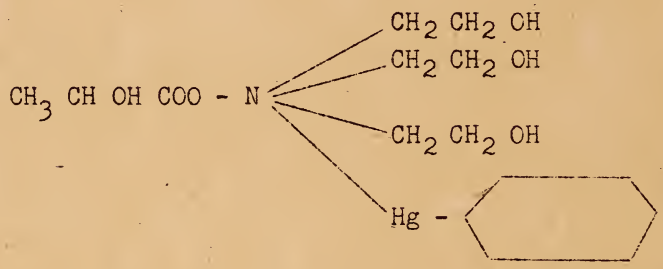
The substituted quaternary ammonium salts stem from the Domagk patent issued in Germany in 1932. Until recently 3 firms were licensed to manufacture in the United States, but in the fall of 1944 some 10 firms had obtained licenses under the Domagk patent and from now on we may expect a great deal of competition in the promotion of this generic group of antiseptic chemicals. The relationship of these compounds to the ammonium ion can be visualized by writing the type structural formula



We may use R_1, R_2, R_3, and R_4 to denote the radicals that may be substituted for the hydrogen attached to the ammonium nitrogen atom and we can denote with the letter X any acid radical that may be attached to the nitrogen. In the most satisfactory members of this group R_1, R_2 are usually short-chained alkyl radicals such as methyl or ethyl. Either, or both, R_3 and R_4 may be long-chain alkyl, aralkyl, substituted aralkyl or aryl radicals. The acid radical X may be a chloride, bromide, fatty acid, nitrile, or rhodanate. In this group, the nitrogen atom serves as the central nucleus to which the non-metallic radicals are attached. When these materials are placed in water most of them readily dissociate into R_{1-4} N cations and X anions; providing us with a cation that is toxic to microorganisms. Since plant and animal surfaces normally carry a nega-

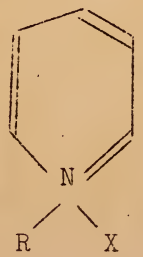
tive charge, it is believed that the positively-charged fungicidal cation may be attracted to and held by such surfaces due to electrostatic phenomena. Compounds typical of this group are benzyl lauryl dimethyl ammonium chloride, dilauryl dimethyl ammonium bromide, lauryl cetyl dimethyl ammonium formate, and oleyl lauryl dimethyl ammonium thiocyanate.

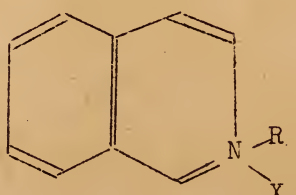
The second generic group of compounds of this class up for discussion are those containing phenyl mercury. These are prepared by reacting phenyl mercury lactate, acetate, or similar salts with triethanol amine. The resulting product, although more complex, is very similar in structure to that in the first group.



It is believed that a phenyl mercury radical is attached to the nitrogen along with 3 ethanol groups to give the cation, and the acid radical (X) is the lactate, acetate, or other anion of the phenyl mercury salt. Formulations in this group have exceedingly high lethal values (L.D.) against fungous spores. Solutions containing 1 to 5 parts per million of these compounds are sufficient to inhibit the germination of Macrosporium sarcinaeforme spores on glass slides. The novel feature of these compounds is their so-called "eradicant" or therapeutic value against fungous pathogens in plant tissues. Owing to their specificity and high fungicidal potency, they have been shown to kill or inhibit fungi that have already established pathogenic relationship with the suscept tissues but without material damage under proper conditions to the latter tissues. While unexcelled for certain uses, members of this group at concentrations of 1:1000 or greater are likely to act as corrosive skin irritants unless promptly washed off. Also, if ingested beyond certain tolerances, they are poisonous.

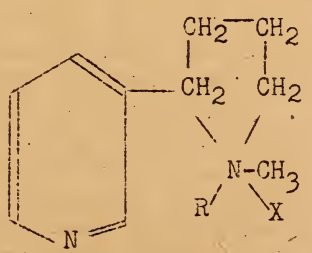
The third generic group encompasses those cationic fungicides that use the 6-membered heterocyclic nitrogen ring as a nucleus; that is, they are monobasic acid derivatives of pyridine, picolines, lutidines, collidines, quinaldines, quinoline, and isoquinoline. Facetiously, they may be termed derivatives of coal, salt, and coconut, since the heterocyclic ring is derived from heavy coal tar oil by distillation, the chlorine of the acid radical may come from salt, and the lauryl (alkyl) radical is extracted from coconuts.





The structural configuration of the molecule in this group is a 6-membered heterocyclic ring, to the nitrogen of which is attached a 10-18 carbon-chain alkyl radical (R) and a halide, thiocyanate, or fatty acid radical (X). Examples of soluble cationic forms are cetyl isoquinolinium bromide, lauryl pyridinium thiocyanate, lauryl quinaldinium bromide, and lauryl isoquinolinium acetate. These compounds are fungitoxic and stable from pH 3 to pH 9, may be manufactured from inexpensive and abundant raw materials, and are reportedly non-poisonous to higher animals. By proper selection of the radical added to the heterocyclic nitrogen nucleus almost any desired degree of surface activity may be obtained and also the solubility of the compound may be varied in oils and in water. This group promises to furnish us with several fungicides that are miscible in and compatible with oil sprays. Toxicant concentrations of 1:5000 in general are adequate as foliage sprays and as antiseptic washes. The compounds are compatible with insecticides and adjuvants except soaps which are not needed for spreading because of the inherent wetting properties of the compounds. Phytotoxicity determinations indicate a considerable margin of safety and it has been found that the molecular structure can be altered to provide varying degrees of resistance to weathering.

The fourth generic group of this quaternary ammonium class is the non-metallic derivatives of nicotine which have proved to be very efficient in the control of fungi. Nicotine has long been employed for combatting insect pests and recently several so-called "fixed nicotine" formulations, such as nicotine bentonite, have appeared. Heretofore these compositions have exerted little or no fungicidal properties. If equal molecular quantities of nicotine and the corresponding alkyl halide such as lauryl bromide are reacted together, a nicotinium derivative represented by the general formula, nicotine (RX), is formed, e. g. lauryl nicotinium bromide. Nicotine is composed of a 6-membered pyridine ring and a 5-membered heterocyclic pyrrolidine which theoretically would permit the atttachment of the R and X radicals to the nitrogen in either ring.



Since the nitrogen of the N-methyl pyrrolidine ring is the more basic, it is assumed that generally the R and X radicals are attached to that ring. In this group of compounds, the mono-valent radical R may be selected from alkyl, aralkyl, or substituted aralkyl radicals. The acid radical X may be an anion selected from the group consisting of chloride, bromide, cyanide, or thiocyanate, or even a fatty acid containing from 2 to 18 carbon atoms. Some of the most promising of these nicotinium derivatives for agricultural use seem to be lauryl nicotinium bromide, cetyl nicotinium thiocyanate, p-nitrobenzyl nicotinium thiocyanate, p-chlorobenzyl nicotinium chloride, and lauryl nicotinium oleate. Perhaps the most remarkable

property of certain members of this group of cationic fungicides is their specificity or great "margin of safety", when used on plant foliage. For example, it has been demonstrated that 60 parts per million of p-nitrobenzyl nicotinium thiocyanate will inhibit the germination of 50 percent of Macrosporium sarcinaeforme spores, and yet it requires a concentration of 17 percent or 170,000 parts per million of this same compound in solution to kill 50 percent of a succulent tomato leaflet dipped in the solution for 5 seconds. In this case, we are using a plant derivative to produce a toxicant for the control of plant pests.

Discussion of the Topic Presented by Dr Howard

In respect to the quaternary ammonium compounds, Dr J. W. Heuberger asked how their tenacity was determined. Dr Howard replied that he had used either the Heuberger technique in which the slide covered with the compound is swished in water, or an unpublished method adapted from a technique used in testing the mildew-proofing value of treatments for textiles, where the treated samples are buried in the soil and are removed at intervals to determine the rate of deterioration in their tensile strength. As adapted to the study of fungicides, the new method involves spraying or dusting the toxicant onto slides coated with cellulose nitrate. The slides are then buried in the soil and individual slides taken out at the start and at intervals of 1, 2, 4, 8, and 16 days to determine how much toxicant remains by means of spore germination response.

In response to the question whether a solid film is formed by these compounds, Dr Howard stated that theoretically there was a monomolecular film. Dr V. L. Frampton asked Dr Howard what made him think that quaternary ammonium compounds form a monomolecular film on a slide. Dr Howard passed the question on to Dr H. H. Mosher, a research organic chemist, who was present. Dr Mosher indicated that this was a tough question, since he had no definite information in regard to the film formed on a plant. He had, however, worked with textiles and with them had obtained evidence that this is the case. Most of these materials react with anions. Anions are present on plant surfaces. These materials often continue to spread in a manner tending toward a monomolecular film.

Dr H. C. Young asked about the toxicity of the Puratized compounds which have mercury present and the problem of tolerance. Dr Howard stated that samples of apples sprayed with such material had been sent for chemical analysis to the Massachusetts Agricultural Experiment Station at Amherst where A.O.A.C. methods were used. The mercury residue ran from 24 to 76 gamma per pound of apple. Chemist J. B. Smith of the Rhode Island Station has written to several chemists for information regarding a method for mercury analysis that is adapted to the purpose. Dr Howard stated that in perhaps two months, data on apple samples obtained from four or five different States would be available for discussion. He called attention, however, to the fact that there was no necessity to use these compounds on edible products. Dr J. G. Horsfall asked why would it not be possible to put zinc in place of mercury in compounds of this type. Dr J. Zender shook his head. Dr Howard stated that he could not answer this and that Dr C. N. Andersen, who could, was not present.

Dr H. W. Thurston remarked that the original Puratized N5X had not proved stable when allowed to stand around the laboratory for a long time. Dr Howard remarked that this material was originally used in the textile trade, which consumed it rapidly so that it did not have a chance to get old enough to show marked deterioration. In working with the material in connection with fungicidal tests, however, it had been found to deteriorate, and this deterioration had been traced to an impurity in the base product. This led to an improvement as a result of which no problem of deterioration had shown up in the material thus far. In a discussion about the nature of the precipitate developing in the material, Dr G. L. Mack remarked that the precipitate did not contain mercury. (H. P. B.)

DITHIOCARBAMIC ACID DERIVATIVES AS FUNGICIDES AND INSECTICIDES

By J. W. Heuberger, Delaware Agricultural Experiment Station
Newark, Delaware

The first investigations of the fungicidal and insectidal value of dithiocarbamic acid derivatives were carried out by the du Pont Company in 1931. In 1934 a patent was obtained by Tisdale & Williams (11) on this group of materials as fungicides. The insecticidal investigations were continued by Guy (4) at the Delaware Agricultural Experiment Station until 1937. This work showed that tetramethyl thiuram disulfide was the most effective feeding inhibitor of the Japanese Beetle and the Mexican Bean Beetle of any material used; ferric dimethyl dithiocarbamate was also quite effective. Later work by Tisdale & Flenner (12) in 1940 and 1941, with improved formulations, showed that ferric dimethyl dithiocarbamate was superior to tetramethyl thiuram disulfide as a Japanese Beetle feeding inhibitor.

While the above insecticidal work was going on, investigations on the fungicidal value of derivatives of dithiocarbamic acid were also being pursued. At the same time, various English workers -- Moore, Montgomery & Shaw (9), Montgomery & Moore (8), Marsh (7) -- also were testing thiuram sulfides as fungicides. They found the disulfide to be slightly more effective than monosulfide in the laboratory and field. Along in the late 1930's the du Pont Company began sending out for preliminary trial as a fungicide samples of a material coded IN-870A3. This was a composition containing 80% technical ferric dimethyl dithiocarbamate, later trade-named Fermate. This was selected for development as a fungicide for several reasons: effectiveness against a wide range of fungi; high effectiveness against diseases previously hard to control; lack of host injury; compatibility with other spray ingredients; high tenacity; and high insectifugal value. Tests by numerous research workers over the country soon showed the value of this compound for the control of numerous plant diseases (1)[1], particularly cedar rust on apple, leaf spot on cherry, anthracnose on tomato, and blue mold on tobacco.

To show the extent of research during the past 2 years on Fermate, and on other dithiocarbamic acid derivatives, papers (3, 12) published in 1942 listed 10 literature citations, while today such citations number more than 120.

Recently, 2 additional dithiocarbamates have been investigated. In 1943, Dimond, Heuberger & Horsfall (2) reported on the fungicidal value of disodium ethylene bisdithiocarbamate, since trade-named Dithane. Heuberger & Manns (6) later showed that the addition of zinc sulfate-lime markedly improved the protective value of this material. The latest addition to the list of dithiocarbamate fungicides is zinc dimethyl dithiocarbamate. During 1944 this material, to the writer's knowledge, has been tested on fruits by Dunegan, of the U. S. Department of Agriculture, and by Winter and Young, of the Ohio Station, and on vegetables by Wilson of the Ohio Station. Also, field experiments testing it on vegetables have been conducted by Heuberger and Wolfenbarger in Delaware. These Delaware tests showed that zinc dimethyl dithiocarbamate gave the best control of tomato anthracnose of any material used, gave as good

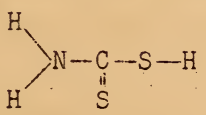
[1] This literature citation is a "List of Publications on Fermate Fungicide. It contains all the citations on the above work.

control of early blight on potato and tomato as did Bordeaux, and was markedly superior to Bordeaux for the control of the potato leafhopper. Data obtained in these tests also showed that, in all respects, zinc dimethyl dithiocarbamate was markedly superior to sodium, calcium, iron, copper, and lead dithiocarbamate as a protective fungicide. No injury of any description was observed on tomatoes and potatoes from zinc dimethyl dithiocarbamate; the copper dimethyl dithiocarbamate injured both.

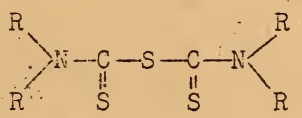
The most complete published study to date of the dithiocarbamates as fungicides is that of Goldsworthy, Green & Smith (3). This research comprised both laboratory and field studies, and was centered on the dimethyl, diethyl, and dibutyl series of metallic dithiocarbamates.

CHEMISTRY OF THE DITHIOCARBAMATES

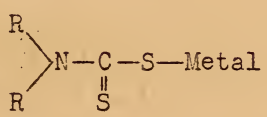
Dithiocarbamic acid has the following formula:



Thiuram sulfide has the following formula:



The metallic dithiocarbamates have the following formula:



PHYSICAL AND CHEMICAL PROPERTIES

Solubility. The dimethyl salts, in general, are more soluble than those of the diethyl and dibutyl series. In the dimethyl series, solubility is as follows (3):

Na salt . . .	>1000 p.p.m.
Fe salt . . .	120 p.p.m.
Zn salt . . .	65 p.p.m.
Pb salt . . .	44 p.p.m.
Cu salt . . .	12 p.p.m.

Stability. The dithiocarbamates are prone to undergo chemical change. The dialkyl dithiocarbamates oxidize very readily. The most usual course is the elimination of dissociable hydrogen from each of 2 molecules, which then combine to form tetralkyl thiuram sulfides which are also effective fungicides.

Under extreme conditions, the zinc salt is more stable to heat and light than the sodium, calcium, and iron salts. Also, these metallic

salts are rather unstable to the action of acids.

Wettability and Tenacity. All the metallic dithiocarbamates require suitable conditioning agents to make them wettable and dispersible for use as fungicides. Except for the water-soluble salts, the tenacity appears to be high.

Compatibility. Research indicates that these compounds are compatible with a wide range of materials. Exceptions are: Fermate in combination with copper has been reported injurious on apples (5): the mercury salt in combination with sulfur is very injurious (unpublished information): Fermate is incompatible with bentonite and lime (3).

pH. The sodium and calcium salts have a basic reaction while the salts of the heavy metals are slightly acid or neutral (3).

FUNGICIDAL AND PHYTOTOXIC VALUES

Considerable research is still needed for a critical evaluation of these properties.

Fungicidal Value. Of the metallic dialkyl dithiocarbamates so far tested, the dimethyl derivatives appear to possess greatest fungicidal value, the diethyl next highest, and the dibutyl least (3). Increase in the carbon chain appears to give lower fungicidal value (10). In the dimethyl series, the soluble sodium salt has been reported (12) to be the most effective in laboratory water dilution tests, the derivatives of a lower degree of solubility in water being less effective.

On apples, the zinc, iron, and lead salts have proved most effective. On vegetables, the zinc salt has proved more effective than the sodium, calcium, iron, lead, or copper salts.

Phytotoxic Value. Based on present available information, it appears that in the dimethyl series the iron, zinc, and lead salts are least phytotoxic when used at fungicidally effective concentrations.

PRESENT STATUS OF DISEASE AND INSECT CONTROL

Thiuram Disulfides

These are not being developed at the moment as general protective fungicides, but as seed protectants (ARASAN) and as turf treatments (THIOSAN). Both of these trade-named materials have as their active ingredient tetramethyl thiuram disulfide.

As Fungicides -- For control of damping-off, of cereal smuts, and turf diseases, such as brown spot and dollar spot.

As Insecticides -- Repellent for Japanese beetle, Mexican bean beetle, Colorado potato beetle, and eastern tent caterpillar; for the control of certain aphids.

Metallic Dithiocarbamates

These materials are being developed primarily as general protective fungicides. They are also fairly good seed protectants.

Ferric Dimethyl Dithiocarbamate (FERMATE) is the best known of the group at present and has been widely tested.

As a Fungicide -- Ferric dimethyl dithiocarbamate has been reported to give control of the following diseases:

Brown rot of sweet cherry
Leaf spot of sweet cherry
Brown rot, rust, and Coryneum blight of peach
Cedar rust and quince rust on apple
Apple scab and apple blotch
Brooks' spot and black rot on apple
Sooty blotch on apple
Pear scab
Cranberry fruit rots
Anthracnose on tomato
Phomopsis blight on eggplant
Bean anthracnose
Celery leaf spots
Tobacco downy mildew
Cabbage downy mildew
Rose mildew and black spot
Various diseases of ornamentals

As an Insecticide -- Repellent for Japanese beetle and Mexican bean beetle.

Disodium Ethylene Bisdithiocarbamate (DITHANE) plus zinc sulfate-lime. This is a recent development and requires further testing.

As a Fungicide -- It is reported to be effective for the control of early blight and late blight on potato, early and late blight on celery.

As an Insecticide -- Reported to be effective for the control of aphis on potato, leafhopper on potato, Mexican bean beetle.

Zinc Dimethyl Dithiocarbamate is a more recent development and has not, as yet, been tested extensively.

As a Fungicide -- It is reported to control early blight and anthracnose of tomato, early blight of potato, apple scab.

As an Insecticide -- It is more effective than Bordeaux for the control of the potato leafhopper.

FUTURE RESEARCH ON PRESENT METALLIC DITHIOCARBAMATES

Considerable research is required along the following lines: fungicidal value; tenacity, stability to heat, light, acids, etc.; protective value in the field; and the phytotoxic range.

SUMMATION

Research on the derivatives of dithiocarbamic acid from 1931 to 1944 has resulted in the development of a seed protectant (Arasan), a turf treatment (Thiosan), and 3 protective fungicides, namely:

Iron dimethyl dithiocarbamate (Fermate)
Zinc dimethyl dithiocarbamate
Disodium ethylene bisdithiocarbamate (Dithane) plus zinc sulfate-lime

In addition to their fungicidal activity, these materials possess considerable insect control value.

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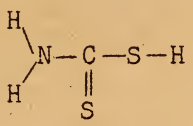
Discussion of the Topic Presented by Dr. Heuberger

After the introductory discussion of the carbamic acid group, Dr Heuberger in answer to a question about the xanthates indicated that these compounds were being worked on by Dr M. C. Goldsworthy of the U. S. Department of Agriculture. Dr Hildebrand asked if a relation exists between thiourea and the dithiocarbamates. Dr Horsfall replied that thiourea has effects somewhat similar but not equal to the latter. In regard to a question about plant injury Dr Heuberger indicated that Dithane plus $ZnSO_4$ was reported by Ruehle as having given some injury on potatoes against which lime exerted a protective effect. Dr J. M.

Hamilton reported that Fermate was not compatible with copper. Dr Young asked whether Fermate acts as a "safener" for lead. Dr A. B. Groves indicated that Fermate depresses the effectiveness of the arsenical. Dr D. H. Palmiter indicated that in his experience there had been some injury from a number of these materials.

Dr Frampton asked how efficient the Heuberger technique is in determining the adherence of fungicides. Asking if the formula



is correct, to which the reply was "Yes", he inquired what the strength of this acid might be. Dr Mack stated that it would be very weak. The answer to Dr Frampton's question, "Have you tried making derivatives by using organic bases?", was "No." Dr Frampton inquired whether the fungicidal effect might be due to dissociation. Dr Heuberger replied that published data regarding dithiocarbamic acid salts indicated that when ionization occurs the fungicidal action at one point on the curve is due to ion action, while at another point it is due to molecular action. Reference was made to the fact that Parker-Rhodes tried to explain this double maximum. Dr Mack pointed out that the absence of breaking-down of dithiocarbamate on weathering would seem to indicate molecular action. Dr A. E. Dimond remarked that the views of Parker-Rhodes based on his experiences were not consistent with the results of studies here. He indicated that the whole question appeared to be in a state of flux at the present time. The question was then asked whether there is any information on the relative solubility of various metal salts of this acid. Dr Heuberger replied that as one goes down in the electromotive series the solubility drops.

Dr Heuberger brought forward figures obtained by Goldsworthy, Green, and Smith on the relative solubility of various metallic salts of carbamic acid in the dimethyl series, as follows:

Sodium salt,	>1000	parts per million
Iron salt,	120	parts per million
Zinc salt,	65	parts per million
Lead salt,	44	parts per million
Copper salt,	12	parts per million

He remarked that available laboratory evidence indicated that the more soluble the salt, the higher it is in fungicidal value, but stated that in the field this cannot be correlated with laboratory findings because the more soluble compounds may wash off while the less soluble materials stick. Also, the factor of stability plays a part in field performance. (H. P. B.)

SYNERGISM AND ANTAGONISM

By James G. Horsfall, Connecticut Agricultural Experiment Station
New Haven

The action of single fungicides is often influenced by the addition of other ingredients such as stickers, spreaders, deposit builders, insecticides, and also other fungicides. The addition of sulfur to Bordeaux mixture has been experimented with since the days of Millardet, but the result is still in doubt. Our ignorance of synergism and antagonism is profound.

Synergism and antagonism are generic expressions to cover the effects of poisons or other ingredients acting jointly. All too often the usefulness of these concepts has been jeopardized by limiting them to cases where the mechanism is mysterious. Such a trend is to be deplored. Synergism, from syn = with, and ergo = to work, means simply to work with. A sticker works with tribasic sulfate to improve its tenacity and presumably thereby its performance. Antagonism is to act against or to work contrariwise. A spreader may act to cause undue run-off and thereby to reduce the effective deposit. It is antagonistic in that sense.

The ingredients in a mixture at equilibrium can act together or oppositely in two basic fashions: (1) to alter the effective dose at any given locus of toxicity, (2) to alter the mechanism of toxicity. The first case may be labelled as supplementary synergism or subtractive antagonism. Two people can push together or against each other in getting a vehicle out of the mire. The second case may be labelled as potentiated action. Instead of merely pushing, they may consult and decide to lift the vehicle out or to pry it out. Conversely, one person may pry in one direction while the other person pushes in the opposite direction.

METHODS OF ASSAYING SYNERGISM AND ANTAGONISM

Often knowledge advances only as fast as the ability to measure. The ability to measure synergism and atagonism is very inadequate because of lack of proper experimental designs. Usually it is not especially difficult to tell that two substances are synergistic or antagonistic. The difficulty is to tell how and how much -- if synergistic, for example, are they supplementary or potentiated, and how much?

If only one ingredient is toxic, the measurement is relatively simple. The effect of the active ingredient can be determined without the second ingredient and in the presence of various amounts of the second ingredient.

The problem of learning how much becomes complex when both ingredients are toxic. The simplest experimental design has resulted perhaps in the most grief. The experimenter tries 2 ingredients separately in single doses and in a 50-50 combination. One produces say 10% kill and the other 50. If the mixture produces more than 60%, it it said to be synergistic; if less than 60%, antagonistic. Such a deduction may be highly misleading. To mix 2 sub-lethal doses to produce synergism or 2 highly lethal doses to produce antagonism may be equally unsatisfactory as a mechanism for measurement. Two elementary facts contribute to this uncertainty: (1) It is statistically indefensible to add and subtract percentages of biological response, as reference to general papers by Bliss or fungicide

papers by Wilcoxon & McCallan will witness. (2) The design does not tell what would happen if the second ingredient were substituted by an equal amount of the first, or if the first ingredient were substituted by an equal amount of the second.

This brings the discussion squarely to the position where the use of the dosage-response tool is imperative. The effect of "how much" can be determined only by using varying dosages. Therefore, it is necessary to use several doses of each ingredient and of the proposed mixtures of ingredients.

Entomologists such as LePelley and Sullivan working on pyrethrum and rotenone for houseflies have used most of that design. They determined the range of equitoxic doses for the 2 ingredients and mixed them 50-50 on the assumption that they would obtain half a response from one ingredient and half a response from the other. This appears to be a reasonably satisfactory design and it was used later by Dimond and Horsfall in studying the interaction between sulfur and copper.

In appraising this design, however, it should be noted that the slopes of the dosage-response curves of the 2 ingredients and of the mixture must all be parallel. LePelley and Sullivan noted that the slopes for the 2 ingredients were parallel. Since they used only a single dose of the mixture, they did not know the slope of the dosage-response curve for it, however. They could not be sure that a 50-50 mixture should have given a response equal to the average of the 2 ingredients.

The significance of changes in slope is as yet unclear, and hence, it will not be dealt with. The significance of slope needs much more research based on models for synergism and antagonism.

It should be said, however, that if the slope of a mixture is different from that of the ingredients, potentiated synergism or antagonism probably has occurred. This probability also needs further research.

An experimental design that offers promise is based on the titration technique of the chemists. A given dose of one ingredient is held constant while the other is varied, instead of reducing one ingredient as the other is increased. With such a design, synergism should be indicated by an increased toxicity with succeeding doses of the second ingredient; antagonism by decreased toxicity. The optimum proportion of ingredients should be indicated by the peak of a bulge for synergism and the floor of a valley for antagonism. In no case so far tried has the result been as simple as that. We have obtained several peaks and valleys. This is disturbing to say the least.

CASES IN PLANT PATHOLOGY

In spite of our meager knowledge of the methods of assaying synergism and antagonism, it will be possible to survey the field very briefly and discuss a few examples that have been developed by methods so far available. The simplest cases that can be authenticated are those where one ingredient is not toxic.

Additive synergism. The use of cottonseed or other oil to improve tenacity of "fixed copper" materials is a classic of additive synergism. The oil maintains a high dose of active ingredient during rains.

Subtractive antagonism. Perhaps the best known case of what seems to be subtractive antagonism is that of the effect of electrolytes such as calcium and magnesium salts on toxicity of copper or mercury. It has been under investigation for some 50 years stemming back at least to Krönig and Paul in the nineties. Recent work at Cornell suggests that the electrolytes seem to compete with the copper for its locus of toxicity and thus to reduce its effective dose. No doubt mercury acts similarly. The work, however, as so far completed, shows that the effect is antagonistic in one range of dose and synergisitic in another range. We have observed a similar effect in other cases where we have attempted to unlock some of the gates hitherto closed to this interesting field. Much more work needs to be done here.

Potentiated synergism. It will be difficult to discuss potentiated synergism and antagonism because our ignorance of the mechanism is profound. A case of apparent potentiated synergism is to be found in the mixture of sulfur and toxic metallic oxides like those of cuprous, cupric, zinc, and lead. Sulfur undoubtedly enhances their potency. The effect is easiest to assay with a non-sulfur-sensitive organism like Macrosporium sarcinaeforme. Any mixture is more potent than an equivalent weight of oxide alone. If a sulfur-sensitive organism like Sclerotinia fructicola is used, however, a bimodal effect occurs, in which antagonism occurs in one range and synergism in another. Presumably, the synergism is to be explained by the formation of metallic sulfide from the metallic oxide since sulfur and oxygen are interchangeable in many compounds. The slope of the curve for the mixture of cuprous oxide and sulfur is steeper than for cuprous oxide alone. It apparently is parallel to that for cuprous sulfide itself. This tends to confirm the feeling that cuprous sulfide is formed.

Potentiated antagonism. We have studied potentiated antagonism with model experiments. If some organic compounds like the dithiocarbamates act by precipitating the metals in spores, then they should be antagonised by metals added to the mixture. The results are intensely interesting but so unorthodox as not to be publishable yet. Here also bimodal curves are the common occurrence. No clear cut case of potentiated antagonism can be cited from the literature.

One interesting study in synergism and antagonism is the case of the interactions of derris and cuprous oxide as investigated by Skaptason on potatoes and by Heuberger and Horsfall on tomatoes.

Cuprous oxide appears to enhance the insecticidal properties of derris dust. Possibly this is an electrostatic charge effect similar to that which supposedly accounts for the action of pyrophyllite on derris. Presumably this is a case of additive synergism.

Derris enhances likewise the potency of cuprous oxide in the control of Alternaria solani. Whether this is a case of supplementary or potentiated synergism is uncertain, but it may be potentiated synergism due to action on two links in a chain. The derris presumably reduces the population of flea beetles which serve to carry spores and to open infection courts.

Antagonism also shows up in this system depending upon the organism. If Phytophthora infestans is involved, the derris is antagonistic to cuprous oxide, not synergistic as in the case of Alternaria solani. The lack of synergism is due to the fact that Phytophthora is not dependent upon flea beetles. The antagonism arises because the proteins in the derris

root combine with copper and thus reduce the dose by subtractive antagonism. No doubt, subtractive antagonism is involved in the instance of derris and cuprous oxide on Alternaria but the antagonistic effect is more than offset by the synergistic effect on the flea beetles.

Therefore, in the same system, cuprous oxide-derris, we have additive synergism on derris, potentiated synergism on the copper, or subtractive antagonism on the copper depending upon the organism concerned.

NEEDED RESEARCH

Considerable research needs doing on the methods of assaying synergism and antagonism. Our knowledge would advance faster than at present, if investigators would try their variables over wide dose ranges when they study such generic problems as "The effect of X on Y in plant pathology." From the data on LD values and slope, much information would accrue on mode of action.

No one, for example, has made a study of the effect on spore inhibition of titrating copper sulfate with lime water. The effect of such titrations on pH has been investigated by chemists in elucidating the composition of bordeaux mixtures. A pathologist with the know-how to make spores "sit up and beg" could make a good contribution here.

Any proposed mode of fungicidal action could be studied in the same way. If, for example, phenylhydrazine inhibits spores by combining with glucose in the cell by the Hinsberg reaction, it could be studied by titrating phenylhydrazine with glucose.

Discussion Following Dr Horsfall's Paper

Following Dr Horsfall's discussion of synergism and antagonism, an invitation was extended to representatives of industries to present anything new they felt free to discuss. No one accepted this invitation. The meeting was also then opened for further free discussion.

Dr G. K. Parris asked if there is any difference in fungicidal action between the dust form and the spray form of any material. He inquired how these new materials should be applied for best results. Dr Young suggested that the use of concentrates and the use of diluents and spreaders should be discussed. In answer to Dr Parris' question, he stated that if it is possible to put on a fungicide so that it stays there it will have the same effect as a dust that it would have as a spray. Inefficiencies of dust have often been due entirely to the sticker or spreader used. He brought out the fact that a dry material can be brought into such a fine state of division that the particles will not adhere to a dry surface. This can hold for an insoluble particulate fungicide.

Dr Heuberger said that several problems are involved in the question of dusting vs. spraying: (1) The problem of getting the spray or dust onto the plants. (2) Getting thorough coverage. In this respect, heavy foliage makes a problem. (3) There is the problem of completeness of film. In mixing up a dust the usual procedure is to add a diluent. For example, fixed copper is mixed with talc or clay. When this mixture is thrown at a plant the film formed is not completely copper. Particles of

copper will be surrounded by particles of the diluent on the surface of the leaf. Where a spray is used, however, every part of the leaf is covered with copper particles. In 1941 Cuprocide was mixed with clay and put through an attrition mill. The thought was to get a better dispersion of copper through the diluent and to crush the copper onto the diluent in such a way that every particle had copper on it. A regularly mixed talc-cuprous oxide dust sample was also put through the attrition mill. With sufficiently prolonged milling these products were as effective in dust form as when applied as a spray.

Dr J. D. Wilson referred to the belief that a good job of dusting is in general as good as a poor job of spraying. The problem of machinery is involved. Spraying is generally better, but Fermate has proved to be an exception, producing, as a dust, results as good as or better than it gives as a spray. Dr Hildbrand asked if this were true under all conditions of surface, etc., to which Dr Young replied, "Yes." (H. P. B.)